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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/759,878 | 01/16/2004 | Samuel Jotham Reich | 129402.00701 | 1285 |

21269 7590 07/08/2008

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| EXAMINER | |
|---|---|
| GIBBS, TERRA C | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 07/08/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/759,878 | REICH ET AL. | |
| | Examiner | Art Unit | |
| | TERRA C. GIBBS | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-59 and 75-87* is/are pending in the application.

4a) Of the above claim(s) *1-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-59 and 75-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *June 9, 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed April 11, 2008.

Claims 32, 34, 35, 40, 55, 75, 86, and 87 have been amended.

Claims 1-59 and 75-87 are pending in the instant application.

This application contains claims 1-31 drawn to an invention nonelected with traverse in the reply filed on August 14, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Accordingly, claims 32-59 and 75-87 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Information Disclosure Statement*

Applicant's information disclosure statement filed June 9, 2008 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

### *Claim Rejections - 35 USC § 112*

In the previous Office Action mailed April 11, 2008, claims 32-59 and 75-87 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicant's Amendment filed April 11, 2008. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to spell out the full name of the adhesion molecule and to correct for a lack in antecedent basis.

## Claim Rejections - 35 USC § 103

In the previous Office Action mailed April 11, 2008 claims 32-59 and 75-87 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,096,722 ('722) in further in view of Hammond et al. (Nature Reviews Genetics 2001, Vol. 2:110-119) and Vickers et al. (Journal of Biological Chemistry, 2003 Vol. 278: 7108-7118, Epub date 2002, Dec 23). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed April 11, 2008.

### *Response to Arguments*

In response to this rejection, Applicants argue that the Examiner's rejection should be withdrawn because the none of the teachings provide an indication of an "effective amount" of siRNA to degrade ICAM-1 mRNA in a human. Furthermore, Applicants argue that the citations identified by the Examiner are completely irrelevant with regard to the effectiveness of siRNA in humans based on the teachings of Hammond as a whole. Applicants point the Examiner to MPEP 2141.02.

These arguments have been fully considered, but are not found persuasive.

First, it should be noted that Applicant's specification, at page 22, second full paragraph discloses:

> "[A]n "effective amount" of the siRNA is an amount sufficient to cause RNAi-mediated degradation of the target mRNA"

Thus, given this general and non-descriptive disclosure, contrary to Applicant's assertions, one of ordinary skill in the art would be able to glean what is an "effective amount" of siRNA to use in the methods as claimed because the "effective amount" only need to simply cause degradation of the target mRNA.

Furthermore, one of ordinary skill in the art would be able to readily determine what is an "effective amount" of siRNA to use in the methods as claimed based on the teachings of the '722 Patent. For example, '722 teaches at column 20, lines 1-9:

> "In the context of this invention, by "therapeutically effective amount" is meant the amount of the compound which is required to have a therapeutic effect on the treated individual. **This amount, which will be apparent to the skilled artisan**, will depend upon the age and weight of the individual, the type of disease to be treated, perhaps even the gender of the individual, and other factors which are **routinely** taken into consideration when designing a drug treatment."

Thus, based on this teaching, it is apparent that determining an "effective amount" of an oligonucleotide-based drug is routine in the art. Therefore, it is the Examiner's position that based on Applicant's general definition of an "effective amount", one of ordinary skill in the art would be able to use the disclosure of the '722 Patent to determine what is an "effective amount" of siRNA to use in the methods as claimed for the degradation of ICAM-1 mRNA.

Second, it should be noted that during examination of the instant application, the Examiner ascertained the differences between the prior art and the claims at issue by

interpreting the claim language and considered both the invention and the prior art references as a whole. In doing so, it has been concluded that the claimed invention, as a whole, would have been *prima facie* obvious. This is particularly true since Hammond et al. discuss that RNAi works in the mouse and are optimistic and discuss the potential of RNAi in humans (see Table 2). Furthermore, Hammond et al. explicitly teach that regarding RNAi in lower organisms (e.g. plants, flies, worms, and fungi) versus higher organisms (e.g. mammals), "[I]t seems probable that the interference mechanism is universal" (see page 117, second to last paragraph).

Applicant is reminded of the recent KSR Decision and principles of the law of obviousness. In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have **reasonably expected** to have been able to do in view of that knowledge. Given the teachings of '772 along with the motivation of Hammond et al., one of ordinary skill in the art would have reasonably expected to be able to devise a method of inhibiting the expression of human ICAM-1 mRNA or to a method of treating complications arising from type I diabetes in a subject comprising administering to a subject in need of such treatment an effective amount of an siRNA comprising a sense RNA strand and an antisense RNA strand, wherein the sense and antisense RNA strands form an RNA duplex, and wherein the sense RNA strand comprises a nucleotide sequence substantially identical to a target sequence in human ICAM-1 such that human ICAM-1 mRNA is degraded as claimed in Applicant's invention.

Applicants next argue that assuming *arguendo* that the skilled artisan could combine the teachings of the '722 Patent, Hammond and Vickers, based on Hammond, preparing an siRNA that effectively targets and degrades any human mRNA would yield unpredictable results and, therefore, successfully using siRNA to inhibit ICAM-1 expression would require undue experimentation and would not yield predictable results.

This argument has been fully considered, but is not found persuasive because as discussed *supra*, Applicant is reminded of the recent KSR Decision and principles of the law of obviousness. In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have **reasonably expected** to have been able to do in view of that knowledge. One of ordinary skill in the art would have reasonably expected success at devising a method of inhibiting the expression of human ICAM-1 mRNA or a method of treating complications arising from type I diabetes in a subject comprising administering to a subject an effective amount of an siRNA comprising a sense RNA strand and an antisense RNA strand, wherein the sense and antisense RNA strands form an RNA duplex, and wherein the sense RNA strand comprises a nucleotide sequence substantially identical to a target sequence in human ICAM-1 such that human ICAM-1 mRNA is degraded. This is primarily based on the fact that the '722 patent teaches the success of such methods using antisense oligonucleotides targeted to human ICAM-1 and Vickers et al. taught that active antisense sites would also be active siRNA sites. Furthermore, one of ordinary skill in

the art would have reasonably expected success at devising a method of inhibiting the expression of human ICAM-1 mRNA or a method of treating complications arising from type I diabetes in a subject comprising administering to a subject an effective amount of an siRNA comprising a sense RNA strand and an antisense RNA strand, wherein the sense and antisense RNA strands form an RNA duplex, and wherein the sense RNA strand comprises a nucleotide sequence substantially identical to a target sequence in human ICAM-1 since KSR forecloses the argument that the substitution of one known element for another would have yielded **predictable results** to one of ordinary skill in the art at the time of the invention. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d).

Applicants next argue that in the Office Actions mailed August 25, 2006 and May 15, 2007, the claims were identified as non-enabled and the Examiner suggested that the use of siRNA to inhibit expression of ICAM-1 would result in unpredictable results. Applicants contend that based on previous non-enablement rejections, an obvious rejection levied by the Examiner requires impermissible hindsight bias based on the Examiner's own admission.

This argument and contention have been fully considered, but are not found persuasive. First, the Examiner acknowledges that in the Office Actions mailed August 25, 2006 and May 15, 2007, the claims were identified as non-enabled. However, after careful reconsideration of the claims, it was determined that the pending claims were enabled by combining teachings found in the prior art, namely the '722 Patent,

Hammond et al., and Vickers et al.

Second, it is noted that it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, at the time the invention was made, the '722 Patent taught and claimed a method of modulating human ICAM-1 expression in a human subject and a method of treating a human subject having a disease or condition associated with abnormal expression of cellular adhesion molecules, such as ICAM-1 comprising administering an antisense oligonucleotide that specifically hybridizes with human ICAM-1 such that human ICAM-1 mRNA is degraded.

'722 did not teach an siRNA molecule. Hammond et al. taught that antisense and RNA interference are two methods of silencing expression of a gene and that RNA interference possesses characteristics that make it superior to antisense. Vickers taught that that positions on target RNA identified as being susceptible for antisense degradation would be coincident with siRNAs designed to bind the same position on the target mRNA. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to devise a method of inhibiting the expression of human ICAM-1 mRNA or a method of treating complications arising from type I diabetes in a subject comprising administering to a subject an effective amount of an siRNA

comprising a sense RNA strand and an antisense RNA strand, wherein the sense and antisense RNA strands form an RNA duplex, and wherein the sense RNA strand comprises a nucleotide sequence substantially identical to a target sequence in human ICAM-1 such that human ICAM-1 mRNA is degraded using the teachings of the '722 patent and following the motivation of Hammond et al. and the motivation and teachings of Vickers et al.

Applicants next contend that they fail to see the relevance of the Vickers reference in the instant rejection. Applicants argue that any disclosure pertaining to RNase H would have no bearing on either siRNA technology or Applicant's pending claims which are directed to methods of using RNA.

This argument has been fully considered, but is not found persuasive. The relevance of the Vickers reference is as follows, and is paraphrased from the instant rejection in the previous Office Action mailed December 11, 2007. Vickers et al. teach that RNAi is considered as an antisense mechanism of action that utilizes a double-stranded RNase to promote hydrolysis of the target RNA. Specifically, Vickers et al. taught that, in general, target sites that are susceptible for antisense degradation are also effective target sites for siRNAs. The results of Vickers et al. concluded that siRNA and antisense oligonucleotides behave similarly in terms of potency, specificity, and efficacy. Thus, the Examiner was relying on Vickers et al. to support the notion that one of ordinary skill in the art would readily accept that antisense oligonucleotides and siRNAs are art-recognized functional equivalents.

Applicants next argue that the ‘722 Patent is not analogous art with the pending

claims because the '722 Patent fails to disclose or even suggest a molecule having a similar structure and function to the siRNA used in the methods as claimed. Applicants contend that the '722 Patent only describes methods of using single-stranded antisense and provides no motivation to prepare double-stranded molecules. Furthermore, Applicants argue that the antisense molecules of the '722 Patent must be chemically modified and based on this, the skilled artisan would expect an unmodified antisense RNA molecule to be degraded when introduced into a living human cell. It is for these reasons that Applicants argue that neither strand of Applicant's recited double-stranded RNA fits within the defined structure of the antisense molecule of the '722 Patent.

In response to Applicant's argument that the double-stranded RNA used in Applicant's invention is nonanalogous art to the antisense molecule used in the '722 Patent, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the instant specification at the Abstract teaches, "RNA interference using small interfering RNAs which are specific for the ICAM-1 gene inhibits expression of this gene". The instant specification at page 5, lines 16 and 17 discloses that siRNAs of the invention specifically target and cause RNAi-induced degradation of mRNA from I-CAM-1 genes. Similarly, the '722 Patent at claim 1 discloses that antisense oligonucleotides are targeted to ICAM-1 mRNA and inhibit gene expression. If this is not convincing enough, Vickers et al. teach that RNAi is

considered as an antisense mechanism of action that utilizes a double-stranded RNase to promote hydrolysis of the target RNA. Specifically, Vickers et al. taught that, in general, target sites that are susceptible for antisense degradation are also effective target sites for siRNAs. The results of Vickers et al. concluded that siRNA and antisense oligonucleotides behave similarly in terms of potency, specificity, and efficacy. Therefore, given either Vickers et al. or Applicant's own disclosure coupled with the disclosure of the '722 Patent, one of ordinary skill in the art would accept on it's face that the double-stranded RNA used in Applicant's invention is analogous art to the antisense molecules used in the '722 Patent.

Regarding Applicant's arguments that the antisense molecules of the '722 Patent must be chemically modified and based on this, the skilled artisan would expect an unmodified antisense RNA molecule to be degraded when introduced into a living human cell, this is not persuasive. This is not found persuasive because Applicant's assertions that the antisense molecules of the '722 Patent must be chemically modified is unfounded. For example, the antisense oligonucleotide claimed in claim 1 and subsequently claimed in the method claims do not comprise any chemical modifications. While the '772 Patent states that modified or substituted oligonucleotides are often preferred over native forms because of desirable properties, this statement is merely a preferred embodiment of the invention disclosed by the '722 Patent. This is particularly true and clear since the antisense oligonucleotide claimed in claim 1 has no chemical modifications.

Applicants finally argue that the '722 Patent does not teach that ICAM-1 is

degraded. Absent such a teaching, Applicants contend that the antisense molecules of the '722 Patent do not have the same function as the double-stranded RNA used in Applicant's claimed invention.

This argument has been fully considered, but is not found persuasive because contrary to Applicant's assertions, the '722 Patent does indeed teach that ICAM-1 is degraded. For example, the '722 Patent discloses in plain language that antisense oligonucleotides are targeted to ICAM-1 mRNA and inhibit gene expression (see claim 1). Furthermore, as Applicant's agree, the '722 Patent teaches, "Hybridization of antisense oligonucleotides with mRNA interferes with one or more of the normal functions of mRNA". Given these disclosures, one of ordinary skill in the art will understand that the antisense oligonucleotides of the '722 Patent degrade ICAM-1 mRNA since (1) claim 1 of the Patent says so in plain language and (2) hybridization of antisense oligonucleotides with mRNA causes degradation of the mRNA through complementary Watson-Crick base pairing. Thus, it is with these teachings that one skilled in the art would accept that the antisense molecules of the '722 Patent indeed have the same function as the double-stranded RNA used in Applicant's claimed invention.

In view of the foregoing, when all the evidence is considered, the totality of the rebuttal evidence of non-obviousness fails to outweigh the evidence of obviousness made of record. Thus, it is maintained that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James "Doug" Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information

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>
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tcg
July 3, 2008

/Sean R McGarry/

Primary Examiner, Art Unit 1635